REMARKS

Applicants have carefully considered the Examiner's Non-Final Office Action, and respectfully request reconsideration of this Application in view of the above Amendment and the following remarks.

Pending in this Application are Claims 1, 4-6, 8-12, 15-20, 36 and 39. Claims 1, 4-6, 8-12, 19, 36 and 39 have been amended.

I. CLAIM REJECTIONS – 35 USC §112

The Examiner has rejected Claim 39 under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner has pointed out that Claim 39 recites in line 19 "the lysosomal storage disorder listed in Table 2", and stated that the claim is indefinite in that it fails to point out what is included or excluded by the claim language.

In response, the Applicants have amended Claim 39 to read as follows:

> 39. (Currently Amended) A method of diagnosing or monitoring a lysosomal storage disorder in a ~~patient~~ subject, comprising:
>
> obtaining a first sample from the ~~patient~~ subject;
>
> measuring a first level of a saposin in the first sample obtained from the ~~patient~~ subject;
>
> comparing the first level to a baseline level, wherein the baseline level is the level of the saposin as determined in a control population of ~~patients~~ subjects unaffected by the lysosomal storage disorder;
>
> determining a presence or extent of a lysosomal storage disorder when the first level is similar or different than the 95th percentile of the baseline level of at least the two saposins in the control population;

wherein,

(i) the similarity of the first level compared to the baseline level is an indicator of absence of the lysosomal storage disorder in the ~~patient~~ subject;

(ii) the difference of the first level compared to the baseline level is an indicator of presence or extent of the lysosomal storage disorder in the ~~patient~~ subject;

(iii) the saposin comprises saposin A, saposin B, saposin C, saposin D;

(iv) the first sample is plasma; and

(v) the baseline level and the first level are about equal to a percent elevation level for the lysosomal storage disorder ~~listed in Table 2.~~

II. CLAIM REJECTIONS – 35 USC §103

Claims 1, 4-6, 8-12, 15-20, 36, and 39 stand rejected as being obvious. In each of the specific rejections, the Examiner has relied upon O'Brien et al. (1991), "Saposin proteins: structure, function, and role in human lysosomal disorders", THE FASEB JOURNAL, vol. 5(3), 301-8 ("the O'Brien Publication") in view of other cited references. Applicants wish to distinguish the teaching of the O'Brien Publication from the currently claimed invention as follows:

A. The Law on Obviousness

1. It is Impermissible to Use Hindsight Picking and Choosing

The Applicants respectfully disagree with the Examiner's view that the method taught in the O'Brien Publication, in view of other cited publications, renders the currently claimed invention obvious. In order for this argument to be valid, the O'Brien Publication would have to provide a link between measuring the accumulation of saposins in subjects with or without LSD and gaining information about LSD. This link was not present in the reference or apparent to one skilled in the art at the time of the invention, as evidenced by the author's own statement on page 306, right hand column, line 67, that says "In each of these storage diseases, studies **need to**

be carried out to determine whether saposin accumulation is of pathophysiological significance" [Emphasis added]. Thus the author himself fails to see this link.

Applicants submit that the reference presents only empirical observations of saposin levels in patients with LSD and also in control subjects. Although Figure 7 of the O'Brien Publication does show levels of saposins in control patients as well as patients with LSDs, it is not indicated that these levels should be compared. To take this information and extrapolate it to the current invention, while ignoring the statement of the author that the link does not exist, constitutes hindsight picking and choosing. This is not proper as held by the Court:

> It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Wesslau, 147 U.S.P.Q. 391, 393 (C.C.P.A 1965)

Thus, isolated observations of saposin levels in subjects with and without LSD does not teach a method for monitoring the disease. In light of the disclosure of the current application, a correlation may be apparent in hindsight, but the author's own statement in the cited references demonstrates that it was not clear to have a link.

2. "Obvious to Try" Does Not Meet the Standard for §103 Obviousness

Modifying the method of detecting saposins in control and experimental samples as described in the O'Brien Publication by using human blood and plasma as described in the Sano Publication, and further extrapolating this to gain information about the state of LSDs may have been obvious to one skilled in the art **to try**, but this does not meet the standard for §103 obviousness as ruled by the Court:

> Obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching suggestion or incentive supporting the combination. At best, in view of the prior art, one skilled in the art might find it **obvious to try** various combinations of these known scale and corrosion prevention agents. This is **not** the standard of 35 U.S.C. §103 [Emphasis added].
>
> *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987)

None of the cited references show directly that measuring levels of saposins in human blood or plasma, followed by comparing these levels to control levels can act as a measure of the presence of LSD. That evidence is first presented in the specification of the current application. As demonstrated in the O'Brien Publication, levels of saposins differ by body compartment in the case of brain, liver, and spleen. It can therefore be expected that levels of saposins in a new body compartment such as blood would be similarly unpredictable. While levels of saposins may be indicative of disease state in tissue samples (although this has not been conclusively shown in the O'Brien Publication), that would not necessarily bear out in an unexamined body compartment such as blood or plasma.

It is not uncommon for a molecular marker of disease to be present at varying levels in different body compartments, only some of which may be indicative or predictive of disease state. For example, tissue samples of breast cancer patients are routinely tested for the biomarker HER-2, which has been found to be indicative of disease prognosis. However, serum levels of HER-2 in patients with metastatic breast cancer have been observed to be only 62% sensitive to tissue HER-2 positivity (please see Kong SY et al. *Clinical Chemistry* 52(8):1510-5, 2006, a copy of the abstract is attached as Exhibit A). In the absence of concrete data, it cannot be assumed that correlations in marker levels and prognostic values will exist between body compartments.

3. Long-Felt, but Unsatisfied Need for the Invention

Finally, the fact that the O'Brien Publication was published in 1989, without any intervening use of the disclosed procedures for the purpose of easing the suffering of those with LSD is further evidence that the current invention was not obvious based on the cited references. As stated in *Graham v. John Deere Co.* 383 U.S. 1 148 U.S.P.Q. 459 (1966), the systematic investigation of nonobviousness includes as relevant evidence the objective indicia of nonobviousness, more recently, called "secondary considerations." These include the long-felt but unsatisfied need for the invention while the needed implementing arts and elements had long been available.

As stated in the specification of the current application, LSDs are a large family of genetic disorders that can lead to the manifestation of severe clinical symptoms. The collective incidence of all lysosomal storage disorders is about 1 in 7000 newborns. This is greater than that of other diseases, such as phenylketonuria, for which newborn screening methods are available. LSDs can be very severe with a wide range of clinical symptoms that include mental retardation, skeletal abnormalities, organomegaly, corneal clouding, and coarse facial features. In recent years treatments for several LSDs have become possible including drug therapy, bone marrow transplantation, and enzyme replacement therapy.

Given that the incidence of the disease is high enough to be of concern (as evidenced by the fact that less frequently occurring diseases have screening tests available), and that therapies are available for patients who are identified as having LSDs, it is clearly desirable to have a screening test for LSDs. As the Examiner has pointed out, the "needed implementing arts" for making the current invention were present, and yet no one had used them to monitor LSDs.

If it had, in fact, been obvious to make this invention using the references cited by the Examiner in this Office Action, one would have expected that such a screening test would have been developed during the past 17 years. Although it is possible to retrospectively observe with benefit of the disclosure in the current application that the available antibody-based technology, antibodies against saposins, and empirical evidence of saposin levels in subjects with LSD could

be used in this manner, it was not obvious to a person skilled in the art at the time of the invention. If it had been obvious, one would imagine that the desire to treat newborns afflicted with the disease would have led to the development and use of such a test.

B. Analysis with Respect to Claims 1, 4, 15, 17, 18 and 39

The Examiner has rejected Claims 1, 4, 15, 17, 18 and 39 under 35 U.S.C. §103(a) as being unpatentable over the O'Brien Publication in view of Sano et al., (1989) "Sphingolipid hydrolase activator proteins and their precursors", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 165 (3), pp. 1191-7, ("the Sano Publication"). Specifically, the Examiner has stated that the O'Brien Publication teaches a method for monitoring lysosomal storage disorder ("LSD") by comparing a measured level of at least one saposin in a tissue sample from a patient to a baseline level, wherein the baseline level is the level of at least the first saposin as determined in a control population of patients unaffected by the lysosomal storage disorder. The Examiner has further stated that the Sano Publication teaches that saposins are not only found in tissues but is also found in human blood and plasma. The Examiner has used this as a basis for considering the current invention obvious over the O'Brien Publication in view of the Sano Publication.

The Examiner has stated that the O'Brien Publication teaches indicating a presence of the lysosomal disorder when the first level exceeds the baseline level, and has therefore rejected Claim 4. As described above, Applicants respectfully disagree with this opinion on the grounds that the O'Brien Publication did not draw a link between saposin levels and the presence of LSD, and that if it had, one would have expected such a test to come into being in the time since the publication of the O'Brien Publication.

The Examiner has stated that the O'Brien Publication teaches the measurement of saposin polypeptide using an antibody in a method which indicates the presence of an LSD when the first level of a saposin exceeds the baseline, and has therefore rejected claim 15. Applicants submit that although the method of the O'Brien Publication teaches using an antibody to measure

saposin levels, it does not describe a link between saposin levels and the monitoring of LSD as has been discussed above.

The Examiner states that the O'Brien Publication teaches the measurement of saposin polypeptide using an antibody immobilized on a solid phase in a method which indicates the presence of an LSD when the first level of a saposin exceeds the baseline, and has therefore rejected Claim 17. Although the O'Brien Publication does teach the use of an immobilized antibody for the measurement of saposins, Claim 17 (including the dependency on Claim 1) describes a method of gaining information about LSD, which is not disclosed in the O'Brien Publication as discussed above.

The Examiner has also rejected Claim 18 on the basis that the O'Brien Publication discloses the measurement of saposin levels in Niemann-Pick disease.

Applicants submit that the O'Brien Publication does not disclose a link between measuring the levels of saposins and gaining information about LSD as discussed.

C. Analysis with Respect to Claims 5, 6, 8-12, 19, 20 and 36

The Examiner has rejected Claims 5, 6, 8-12, 19, 20 and 36 under 103(a) as being unpatentable over O'Brien in view of Sano et al., in further view of U.S. Patent No 6,376,236 to Dubensky et al. ("the Dubensky Patent"). This is based on the Examiner's assertion that the O'Brien Publication discloses the correlation between saposin levels and Gaucher's disease (an LSD), that the Sano Publication discloses the presence of saposins in blood, and that the Dubensky Patent discloses that treatment exists for LSDs.

As described above, the Applicants submit that, although the O'Brien Publication discloses empirical measurements of saposin levels in subjects with and without LSD, the link to using this information to gain information about LSD is not present or obvious in view of the O'Brien Publication. As the Examiner has pointed out:

"...neither O'Brien nor Sano specifically teach the step of monitoring the progression of the disease (claim 5), the patient undergoing treatment for the lysosomal storage disorder (claim 6), selecting a patient that is not known to have a lysosomal storage disorder before the measuring step; selecting a patient that is an infant (claim 9) or fetus (claim 10), (claim 11), nor the step of determining a treatment program (claims 19 and 20), nor the indication of positive treatment (claims 5, 11 and 12)."

As discussed above, these claims require a link between saposin levels and information about LSD which is neither disclosed, nor suggested, by the O'Brien Publication. Although the Dubensky Patent discloses that methods for treating a specific LSD exist, this would not be sufficient to overcome the absence of this link.

D. Analysis with Respect to Claim 16

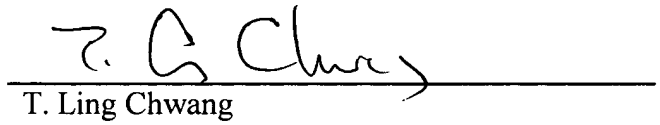
The Examiner has further held that Claim 16 is unpatentable over the O'Brien Publication in view of Sano et al., in further view of Stastny et al. (1992), "Production and Characterization of a Monoclonal Antibody to Human Saposin C", HYBRIDOMA, vol. 11, 351-359 ("the Stastny Publication"). The Examiner has stated that the O'Brien Publication in view of the Sano Publication discloses the invention substantially, while the Stastny Publication discloses a monoclonal antibody which reacts with saposin C.

Applicants respectfully submit that the O'Brien Publication does not disclose the invention substantially because it does not draw a link between measuring levels of saposins and gaining information about LSD as discussed above. As such, even in combination, the O'Brien Publication and the Stastny Publication still falls short of the claimed invention.

III. CONCLUSIONS

Applicants respectfully submit that, in light of the foregoing Amendment and comments, Claims 1, 4-6, 8-12, 15-20, 36, and 39 are all in condition for allowance. A Notice of Allowance is therefore requested for all claims. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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